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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/885,287	06/21/2001	Andreas Sewing	MERCK-2261	2670

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EXAMINER	
GOLLAMUDI, SHARMILA S	
ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 05/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/885,287	SEWING ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 21* is/are pending in the application.

4a) Of the above claim(s) *11-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Amendments and Arguments filed February 25, 2005 is acknowledged. Claims **1-8, 10-19, 21, and 23-27** are pending in this application.

Election/Restrictions

The Restriction Requirement of 7/26/02 is withdrawn in view of applicant's amendments to the withdrawn claims. However, the examiner retains the right to go final since applicant has amended the withdrawn claims to depend on the elected invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Rejection of claims 1-3 and 5-6 under 35 U.S.C. 102(b) as being anticipated by Sauk et al (4,780,450) is withdrawn in view of the amendments of 2/25/05 claiming a coated metallic implant.

Rejection of claims 1-3 and 5-8 under 35 U.S.C. 102(b) as being anticipated by Geistlich et al (5,573,771) is withdrawn in view of the amendments of 2/25/05 claiming a coated metallic implant.

Claims 1-3, 5, 10-16, 18-19, 21, 23, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Worch et al (6,524,718).

Worch et al disclose a metallic substrate (titanium) having a polyphase oxide coating. The polyphase coating has a metal oxide and at least one other organic or inorganic phase. See abstract. The process of coating the implant yields a two-layer oxide coating, where the outer layer is the inorganic and/or the organic phase. See column 2, lines 32-45. The inorganic component is calcium phosphate and the organic component is Type I collagen. See column 2, lines 46-60. Claim 1 envisages a combination of an organic phase and inorganic phase and claim 4 envisages calcium phosphate as the organic phase. Example 1 discloses a coating thickness of 250 nm (.250 micrometers). Worch discloses a process wherein the metallic implant is immersed in a collagen solution at the instant pH and temperature and then coated again with a phosphate solution. Note that the use of calcium ions in this solution is clearly envisaged as noted in column 2, lines 46-60 and claim 4.

Note that the recitation "wherein the coating is obtained by precipitating phosphate from a solution in the presence of collagen" and process limitation in claims 11-19 are product-by-process limitation. According to the MPEP section 2113, "even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985).

With regard to claim 3, collagen in combination with mineral components implicitly tends to separate phases or layers. US Patent 5,543,441 column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner's argument.

Response to Arguments

Applicant argues that Worch describes an electrochemical coating process, which forms a two-layered system, wherein the outer layer comprises an organic and/or inorganic phase. Applicant argues that the coating of Worch are embedded in the oxide surface of the implant and not deposited on the implant surface. Applicant argues that Worch does not describe the process for producing a mineralized collagen matrix.

Applicant's arguments filed 2/25/05 have been fully considered but they are not persuasive. Firstly, it is pointed out that the claims are merely directed to a coated metallic implant that comprises an outer layer of a collagen matrix mineralized with calcium phosphate. It is further pointed out that the claim language is open, i.e. comprising. Thus, the instant claims neither excludes the additional oxide layer nor do the claims recite that the instant coating composition is directly deposited on the implant. Thus, Worch still reads on the instant claims since Worch discloses an outer layer that comprises an organic (specifically collagen) and/or inorganic phase (specifically calcium phosphate) coated on a metallic implant.

With regard to the product-by-process claims, i.e. independent claim 11, the examiner points out that "even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985). Further in instant case, Worch discloses a substantially similar process wherein the metallic implant is immersed in a collagen solution at the instant pH and temperature and

then coated again with a phosphate solution. Therefore, it is the examiner's position that the coated implant, i.e. **the product**, would be the same absent evidence of the contrary. Further, although applicant argues that the instant process yields a different product with a permeable structure analogous to bone and has compared the instant invention with *Shirkanzadeh*, the applicant has not compared the instant product with the prior art structure of Worch et al.

For the above reasons, the rejection is maintained.

Claims 1-4, 10-16, 18-19, 21, 23, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Shirkanzadeh (5,205,921).

Shirkanzadeh discloses a method of depositing bioactive coatings on conductive substrates wherein a cathode and D.C. potential is applied to raise the interfacial pH at the cathode sufficiently enough to precipitate the desired oxide or phosphate thereon as a dense adherent film. See abstract. The substrate can be titanium alloy or steel and the coating is 50 microns thick for a uniform, continuous, and firmly bonded coating. See example 4. The coating composition includes calcium phosphate and non-toxic biological compounds, i.e. collagen. The inorganic compounds, i.e. calcium phosphate, may be co-precipitated with the organic compounds, i.e. collagen. This process allows the doping of specific ions in calcium phosphate crystals. See column 3, lines 5-20. Preferably crystalline calcium phosphate is utilized compared to amorphous calcium phosphate. The particle range of the calcium phosphate is 2-5 microns. See example 2. The micropores in the calcium phosphate compound coating also encourages better adhesion of collagen. The instant doping agents (carbonate and fluoride) are taught in the electrolyte solution.

Note that the recitation "wherein the coating is obtained by precipitating phosphate from a solution in the presence of collagen" and process limitation in claims 11-19 are product-by-process limitation. According to the MPEP section 2113, "even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985).

With regard to claim 3, collagen in combination with mineral components implicitly tends to separate phases or layers. US Patent 5,543,441 column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner's argument.

Response to Arguments

Applicant argues that Shirkanzadeh teaches a calcium phosphate layer that encourages adhesion of macromolecules such as collagen. Applicant argues this structure is too large to promote mineralization since Shirkanzadeh's crystal sizes are too large to promote mineralization. Applicant submits Figure 1, which shows the structure of Shirkanzadeh and submits Figure 3 as the instant invention wherein the crystal sizes are less than 1 micron.

Applicant's arguments filed 2/25/05 have been fully considered but they are not persuasive. Firstly, the examiner points out that independent claim 1 does not recite any process steps, which provide this "unique structure". The claims broadly recites a metallic implant coated with "a bone analogous coating comprising a collagen matrix mineralized with a calcium phosphate phase. It is further pointed out that claims are given their broadest reasonable

interpretation. Mineralize is defined by Merriam-Webster's Collegiate Dictionary as: "to impregnate or supply with mineral". Thus, the claims merely requires that the coating composition comprises collagen and calcium phosphate, since the very addition of calcium phosphate to collagen is sufficient to meet to limitation "mineralized".

With regard to the product-by-process limitations, the examiner points out that Shirkanzadeh teaches a substantially similar process wherein the metallic implant in an aqueous solution having a pH of less than 8 and contains calcium phosphate and is co-precipitated with collagen. The examiner points out that applicant claims the co-precipitating collagen and calcium phosphate in independent claim 11. The examiner points out that if the applicant asserts that a certain process in product-by-process claims provide the novel structure, then the applicant must claim the patentably distinct process that yields the inventive product. The applicant in instant case has not done so.

With regard to the crystal particle size, it is noted that the features upon which applicant relies are not recited in the rejected claim(s) except for claim 24. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

For the above reasons, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 5, 7-8, 17, and 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Kwan et al (5776193).

Shirkanzadeh discloses a method of depositing bioactive coatings on conductive substrates wherein a cathode and D.C. potential is applied to raise the interfacial pH at the cathode sufficiently enough to precipitate the desired oxide or phosphate thereon as a dense adherent film. See abstract. The substrate can be titanium alloy or steel and the coating is 50 microns thick for a uniform, continuous, and firmly bonded coating. See example 4. The coating composition includes calcium phosphate and non-toxic biological compounds, i.e. collagen. The inorganic compounds, i.e. calcium phosphate, may be co-precipitated with the organic compounds, i.e. collagen. This process allows the doping of specific ions in calcium phosphate crystals. See column 3, lines 5-20. Preferably crystalline calcium phosphate is utilized compared to amorphous calcium phosphate. The particle range of the calcium phosphate is 2-5 microns. See example 2. The instant doping agents (carbonate and fluoride) are taught in the electrolyte solution.

The reference does not specify the type of collagen utilized, the diameter of the calcium phosphate crystals, or drugs.

Kwan et al teach a mineralized Type I collagen matrix containing calcium phosphate for bone grafting. Kwan teaches the suitability of collagen or collagen derivatives for the matrix, with a preference for Type I. The matrix may contain other agents such as growth factors, calcitonin, and binders such as gelatin. See column 3, lines 56-65 and column 4, lines5-10. By utilizing drugs such as growth factors in the matrix, the matrix may also provide a substrate to which the host's growth factors may bind and facilitate repair. See column 5, lines 46-60. Kwan teaches that the particles are of an average diameter of less than five microns since these particles are small enough to phagocytized to stimulated local reaction and further bone resorption. See column 5.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings Shirkanzadeh et al and Kwan et al since both teach collagen matrix containing calcium phosphate. One would be motivated to look to the guidance of Kwan et al and utilize instant collagen type since the instant collagen type is recognized as suitable material for implants.

Further, one would be motivated to utilize instant active agents such as growth factors to facilitate repair. Therefore, the selection of the pharmaceutical contained in the implant depends on the intended use of the implant and the treatment plan.

Lastly, it is deemed obvious to one of ordinary skill in the art at the time the invention was made to manipulate the parameters of particle size of the calcium phosphate thorough routine experimentation, absent evidence to the contrary. Additionally, one would be motivated to utilize the instant diameter range since Kwan teaches the utilization of particles with less than 5 microns to further bone resorption.

Claims 6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Sauk et al (4,780,450).

Shirkanzadeh discloses a method of depositing bioactive coatings on conductive substrates wherein a cathode and D.C. potential is applied to raise the interfacial pH at the cathode sufficiently enough to precipitate the desired oxide or phosphate thereon as a dense adherent film. See abstract. The substrate can be titanium alloy or steel and the coating is 50 microns thick for a uniform, continuous, and firmly bonded coating. See example 4. The coating composition includes calcium phosphate and non-toxic biological compounds, i.e. collagen. The inorganic compounds, i.e. calcium phosphate, may be co-precipitated with the organic compounds, i.e. collagen. This process allows the doping of specific ions in calcium phosphate crystals. See column 3, lines 5-20. Preferably crystalline calcium phosphate is utilized compared to amorphous calcium phosphate. The particle range of the calcium phosphate is 2-5 microns. See example 2. The instant doping agents (carbonate and fluoride) are taught in the electrolyte solution.

The reference does not specify the instant collagen combination, i.e. type I and type III.

Sauk et al disclose a composition containing particulate calcium phosphate (hydroxyapatite) and type I collagen (col. 4, lines 59-66). A mixture of type I and type III collagen is taught (example 1). Sauk et al disclose in column 2, line 60 to column 3, line 5, "the composition preferably comprise a mixture of phosphophoryn calcium, a matrix material (type I collagen), and calcium phosphate ceramic. These compositions are intended to facilitate matrix-mediated mineralization, whereby the collagen defines a structural matrix and the salt regulates

and directs mineral deposition in terms of its location, crystallinity and association with the calcium phosphate ceramic particles.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of Shirkanzadeh et al and Sauk et al and utilize a mixture of type I and type II collagen for the collagen matrix. One would have been motivated to do so since, as indicated by Sauk et al, this is a routine practice done at the time the invention was made.

Claims 1-3, 5, 7-8, 10-19, 23, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rhee et al (5,543,441).

Rhee et al teach solid implants coated with collagen-polymer conjugates, which may contain particulates such as calcium phosphate. The dried collagen-PEG composition has sponge-like properties and when incorporated with growth factors, serve as an effective controlled-release device. See column 7, lines 1-6. Example 7 teaches a coating composition contain collagen (Type I) and hydroxyapatite/tricalcium phosphate or gelatin beads (example 7 and claim 9). Rhee teaches the collagen-polymer and HA+TCP (hydroxyapatite and tricalcium phosphate) exhibits high tensile strength. Example 5 discloses coating a titanium implant with the coating composition of the inventive collagen- polymer conjugate, however calcium phosphate is not used in coating composition of this example.

Although Rhee teaches the instant coating composition, example 7's coating composition is not specifically utilized to coat a metal implant.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to look to the guidance provided by Rhee et al and utilize the coating composition of

example 7 to coat the metallic implant of example 5. One would have been motivated to do so since although Rhee does not exemplify this embodiment, Rhee clearly suggests the use of the inventive collagen-polymer conjugate with particulates such as HA and TCP for coating implants. Therefore, the instant invention is prima facie obvious in view of the general disclosure of Rhee et al.

Note that the recitation "wherein the coating is obtained by precipitating phosphate from a solution in the presence of collagen" and process limitation in claims 11-19 are product-by-process limitation. According to MPEP section 2113, "even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985).

With regard to claim 3, collagen in combination with mineral components implicitly tends to separate phases or layers. US Patent 5,543,441 column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner's argument.

Response to Arguments

Although Rhee has been changed to an obviousness rejection in view of the amendment of 2/25/05, the merits of Rhee will be discussed below since Rhee is considered to render the instant invention obvious.

Applicant argues that Rhee teaches an implant coated with a collagen-polymer conjugate, which may be combined with calcium phosphate.

Applicant's arguments filed 2/25/05 have been fully considered but they are not persuasive. The examiner points out that the claims recite open claim language, i.e. comprising. Thus, the scope of the claims does not exclude the use of the polymer conjugate. Secondly, it should be noted that example 7 compares a prior art formulation that contains collagen and calcium phosphate. Therefore, it is clear that a coating composition containing collagen and calcium phosphate are known in the art.

Further, it is noted that applicant asserts that the instant process yields a substantially different product. However, the examiner points out that independent claim 1 does not recite any process steps, which provides this "unique structure". The claims broadly recite a metallic implant with "a bone analogous coating comprising a collagen matrix mineralized with a calcium phosphate phase." It is further pointed out that claims are given their broadest reasonable interpretation. Mineralize is defined by Merriam-Webster's Collegiate Dictionary as: "to impregnate or supply with mineral". Thus, the scope of the claim merely requires that the coating composition comprise collagen and calcium phosphate, since the very addition of calcium phosphate to collagen is sufficient to meet to limitation "mineralized".

With regard to independent claim 11 and those the rejected dependent claims, the examiner points out "even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985). Although applicant argues that the instant process yields a

permeable structure analogous to bone and has compared the instant invention with *Shirkanzadeh*, the applicant has not compared the instant product with the prior art structure of Rhee et al. Therefore, the examiner cannot determine if the instant process does in fact yield a different product from the prior art, Rhee et al.

For the above reasons, the rejection is maintained.

Conclusion

None of the claims are allowed at this time.

Applicant's amendments of 2/25/05 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sharmila S. Gollamudi
Examiner
Art Unit 1616

SSG

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